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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Woonza M. RHEE et al.

Serial No.: Con. of 09/733,739 — Group Art Unit: Unassigned

Filing Date: Filed herewith — Examiner: Unassigned

Title: CROSS-LINKED POLYMER COMPOSITIONS AND METHODS FOR THEIR USE

## PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

This is a preliminary amendment to the patent application identified above, a continuation of U.S. Serial No. 09/733,739, filed December 8, 2000. Prior to examination of the application, please enter the amendments indicated in Appendix A and explained herein.

## AMENDMENTS

**IN THE SPECIFICATION:**

On page 1, please amend the section at lines 13-16 as indicated in Appendix A. The new section will read as follows:

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Serial No. 09/733,739, filed December 8, 2000, which is a continuation of U.S. application Serial No. 09/302,852, filed April 30, 1999 and issued as U.S. Patent No. 6,166,130 on December 26, 2000, which was a continuation of U.S. application Serial No. 09/229,851, filed January 13, 1999 and issued as U.S. Patent No. 6,051,648 on April 18, 2000, which was a continuation of U.S. application Serial No. 08/769,806, filed December 18, 1996 and issued as U.S. Pat, No. 5,874,500 on February 23, 1999, which was a continuation-in-part of U.S. application Serial No. 08/573,799, filed December 18, 1995, now abandoned, all of which applications are incorporated herein by reference in full, and to which we claim priority under 35 U.S.C. §120.

## IN THE CLAIMS:

Please cancel claims 1, 2 and 5-65 without prejudice.

Amend claims 3 and 4 as indicated in Appendix A. The amended claims will then read as follows:

3. (Amended) The composition of claim 66, wherein n = 2.

4. (Amended) The composition of claim 66, wherein m = 2.

Add new claims 66-131 as indicated in Appendix A.

## REMARKS

This is a preliminary amendment to the continuation application filed concurrently herewith. Applicants have amended the specification and claims as indicated above, and as more particularly set forth in Appendix A. The amendments are explained below.

### THE AMENDMENT TO THE SPECIFICATION:

The application has been amended to identify this application as a continuation of U.S. Serial No. 09/733,739 and update the chain of priority back to the originally filed application in this family, U.S. Serial No. 08/573,799, filed December 18, 1995.

### THE CLAIM AMENDMENTS AND NEW CLAIMS:

With the above amendments, claims 1, 2 and 5-65 have been canceled, new claims 66-131 have been added, and claims 3 and 4 have been amended so as to depend from new claim 66. Accordingly, claims 3, 4 and 66-131 are now pending.

The new claims are as follows:

Claims 66-86: These claims are directed to a crosslinkable composition comprised of two crosslinkable components that are biocompatible, synthetic, and nonimmunogenic, wherein the first crosslinkable component has m nucleophilic groups, wherein $m \geq 2$, the second crosslinkable component has n electrophilic groups capable of reaction with the m nucleophilic groups to form covalent bonds, wherein $n \geq 2$ and $m + n \geq 5$, and crosslinking of the composition results in a biocompatible, nonimmunogenic, crosslinked matrix. Addressing these claims in order, support for the terminology used therein may be found in the specification as filed as follows: claim 66 - page 5, lines 8 and 19, and page 6, line 26 ("components"); claim 66 - page 9, lines 13-14 and 20-23 ("synthetic"); claim 66 - page 6, lines 21-25 (nucleophilic groups and electrophilic groups are capable of "covalently binding" to each other); claim 66 - page 7, lines 7-8 ($m \geq 2$, $n \geq 2$, and $m + n \geq 5$); claim 66 - page 5, lines 6-7 ("biocompatible" and "nonimmunogenic"); claims 67-74 - page 7, lines 15-18 (the electrophilic groups may be the same or different; the nucleophilic groups may be the same or

different); claim 75 - page 9, line 21 ("not naturally occurring"); claims 76 and 77 - page 7, line 27 - page 8, line 25 ("linking groups"); claims 78 and 79 - pages 12-15 (hydrophilic polymers, hydrophobic polymers); claim 80 - page 7, line 8 and throughout ("the m nucleophilic groups are primary amino groups"); claim 81 - page 11, lines 24-26 ("first crosslinkable component is $C_2$-$C_6$ hydrocarbyl substituted with amino groups"); claim 82 - page 11, lines 27-28 ("first crosslinkable component is a secondary or tertiary amine $NR_1R_2R_3$ wherein $R_1$ is hydrogen or an amino-substituted lower alkyl group, and $R_2$ and $R_3$ are amino-substituted lower alkyl groups"); claims 83 and 84 - page 7, lines 10-11 ("the n electrophilic groups are selected from the group consisting of succinimidyl ester, sulfosuccinimidyl ester, maleimido, epoxy, isocyanato, thioisocyanato, and ethenesulfonyl"); claim 85 - page 7, line 8 and throughout ("the m nucleophilic groups are sulfhydryl groups"); and claim 86 - page 7, line 8 through page 8, line 24 (reaction of a sulfhydryl moiety with a sulfhydryl-reactive group to form a thioester, thioether or disulfide linkage).

Claims 87-92, 120, 122 and 126-128: These claims are drawn to a crosslinkable system wherein the crosslinkable components are physically segregated, to a method for preparing a biocompatible, nonimmunogenic, crosslinked matrix, to the matrix prepared thereby, to a crosslinkable system wherein one of the two components is present at a molar excess relative to the other, and to a crosslinkable composition containing an imaging agent. Support is as follows: claim 87, 89, 91 and 92 - "components," "synthetic," "covalent binding," "biocompatible," "nonimmunogenic," as above; claim 87 - page 17, lines 18-30 and page 22, lines 12-20 (components are stored separately and are thus "physically segregated"); claims 88 and 90 - page 17, lines 29-30 (the first crosslinkable component is in an aqueous solution); claims 120 and 122 - page 23, lines 8-27 (regarding compositions containing one crosslinkable component in molar excess relative to the other); claim 126 - pages 17-18, bridging paragraph (regarding imaging agents); and claims 127-128 - page 24, line 4 - page 25, line 26 (compositions used for delivery of biologically active agents).

Claims 93-119, 121, 123-125, and 129-131: These are method of use claims, with dependent product-by-process claims, and are supported as follows: claims 93-97 - page 4,

lines 4-10 and page 27, line 4 - page 29, line 29 ("nonsurgical attachment" of a first surface to a second surface); claims 98-100 - claims 36-41 as filed, page 22, lines 3-27; claims 101-103 - page 31, lines 1-21 (prevention of adhesions "following surgery or injury"); claims 104-108 - page 30, lines 1-29 (tissue augmentation); claims 109-119 - page 31, line 22 - page 32, line 13 (regarding coating of synthetic implants), and page 29, lines 3-8 (additional description regarding specific implants); claims 121 and 123-125 - page 23, line 8 - page 24, line 3 (regarding preparation of a matrix for delivering a charged compound); claims 129 and 130 - page 32, lines 14-21 (use in treating vascular malformations); claim 131 - page 33, lines 3-14 (use in coating the interior of a physiological lumen).

Accordingly, no new matter has been added, and entry of the claim amendments and new claims is thus proper and respectfully requested.

## CONCLUSION

Applicants request a timely first Action concerning the subject application. Should the Examiner have any questions concerning the application or this amendment, please contact the undersigned attorney at (650) 330-0900.

Respectfully submitted,

Date: 8/17/01

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## APPENDIX A

## REDACTED SPECIFICATION AND CLAIMS INDICATING AMENDMENTS MADE IN THIS RESPONSE

**IN THE SPECIFICATION:**

On page 1, please amend the section at lines 13-16 as follows:

**~~CROSS-REFERENCES~~ CROSS-REFERENCE TO RELATED APPLICATIONS**

This application is a continuation of U.S. application Serial No. 09/733,739, filed December 8, 2000, which is a continuation of U.S. application Serial No. 09/302,852, filed April 30, 1999 and issued as U.S. Patent No. 6,166,130 on December 26, 2000, which was a continuation of U.S. application Serial No. 09/229,851, filed January 13, 1999 and issued as U.S. Patent No. 6,051,648 on April 18, 2000, which was a continuation of U.S. application Serial No. 08/769,806, filed December 18, 1996 and issued as U.S. Pat. No. 5,874,500 on February 23, 1999, which was a continuation-in-part of U.S. application Serial No. 08/573,799, filed December 18, 1995, now abandoned, all of which ~~application is~~ applications are incorporated herein by reference in full, and to which we claim priority under 35 U.S.C. §120.

**IN THE CLAIMS:**

Cancel claims 1, 2 and 5-65 without prejudice.

Amend claims 3 and 4 as follows:

3. (Amended) The composition of claim ~~2~~ 66, wherein ~~m is greater than or equal to two, and~~ n = 2.

4. (Amended) The composition of claim ~~2~~ 66, wherein m = 2, ~~and n is greater than or equal to 2~~.

Please add the following new claims 66-131:

66. A crosslinkable composition comprised of:

(a) a first crosslinkable component having m nucleophilic groups, wherein $m \geq 2$;

(b) a second crosslinkable component having n electrophilic groups capable of reaction with the m nucleophilic groups to form covalent bonds, wherein $n \geq 2$ and $m + n \geq 5$,

wherein each of the first and second crosslinkable components is biocompatible, synthetic, and nonimmunogenic, and crosslinking of the composition results in a biocompatible, nonimmunogenic, crosslinked matrix.

67. The composition of claim 66, wherein the m nucleophilic groups are identical.

68. The composition of claim 66, wherein at least two of the m nucleophilic groups are different.

69. The composition of claim 66, wherein the n electrophilic groups are identical.

70. The composition of claim 67, wherein the n electrophilic groups are identical.

71. The composition of claim 68, wherein the n electrophilic groups are identical.

72. The composition of claim 66, wherein at least two of the n electrophilic groups are different.

73. The composition of claim 67, wherein at least two of the n electrophilic groups are different.

74. The composition of claim 68, wherein at least two of the n electrophilic groups are different.

75. The composition of claim 66, wherein the first and second crosslinkable components are non-naturally occurring, synthetic molecules.

76. The composition of claim 66, wherein the m nucleophilic groups are bound to the first crosslinkable component through linking groups.

77. The composition of claim 66, wherein the n electrophilic groups are bound to the second crosslinkable component through linking groups.

78. The composition of claim 66, wherein at least one of the first and second crosslinkable components is comprised of a hydrophilic polymer.

79. The composition of claim 66, wherein one of the first and second crosslinkable components is comprised of a hydrophobic polymer.

80. The composition of claim 66, wherein the m nucleophilic groups are primary amino groups.

81. The composition of claim 80, wherein the first crosslinkable component is $C_2$-$C_6$ hydrocarbyl substituted with amino groups.

82. The composition of claim 80, wherein the first crosslinkable component is a secondary or tertiary amine $NR_1R_2R_3$ wherein $R_1$ is hydrogen or an amino-substituted lower alkyl group, and $R_2$ and $R_3$ are amino-substituted lower alkyl groups.

83. The composition of claim 80, wherein the n electrophilic groups are selected from the group consisting of succinimidyl ester, sulfosuccinimidyl ester, maleimido, epoxy, isocyanato, thioisocyanato, and ethenesulfonyl.

84. The composition of claim 83, wherein the n electrophilic groups are selected from the group consisting of succinimidyl ester and sulfosuccinimidyl ester.

85. The composition of claim 66, wherein the m nucleophilic groups are sulfhydryl groups.

86. The composition of claim 85, wherein the n electrophilic groups are sulfhydryl-reactive groups selected so as to form a thioester, thioether, or disulfide linkage upon reaction with the sulfhydryl groups.

87. A crosslinkable system comprised of

(a) a first crosslinkable component having m nucleophilic groups, wherein $m \geq 2$; and

(b) a second crosslinkable component having n electrophilic groups capable of reaction with the m nucleophilic groups to form covalent bonds, wherein $n \geq 2$ and $m + n \geq 5$,

wherein each crosslinkable component is biocompatible, synthetic, nonimmunogenic, and physically segregated from the other crosslinkable component, and crosslinking of the two components results in a biocompatible, nonimmunogenic, crosslinked matrix.

88. The crosslinkable system of claim 87, wherein the first crosslinkable component is in an aqueous solution.

89. A method for preparing a biocompatible, nonimmunogenic, crosslinked matrix, comprising admixing, under crosslinking conditions, (a) a first crosslinkable component having m nucleophilic groups, wherein $m \geq 2$, with (b) a second crosslinkable component having n electrophilic groups capable of reaction with the m nucleophilic groups to form covalent bonds, wherein $n \geq 2$ and $m + n \geq 5$, wherein each of the first and second crosslinkable components is biocompatible, synthetic, and nonimmunogenic, and crosslinking of the components results in a biocompatible, nonimmunogenic, crosslinked matrix.

90. The method of claim 89, wherein the first crosslinkable component is in an aqueous solution.

91. The biocompatible, nonimmunogenic, crosslinked matrix prepared by the method of claim 89.

92. The biocompatible, nonimmunogenic, crosslinked matrix prepared by the method of claim 90.

93. A method for effecting the nonsurgical attachment of a first surface to a second surface, comprising:

(a) providing a first crosslinkable component having m nucleophilic groups, wherein $m \geq 2$;

(b) providing a second crosslinkable component having n electrophilic groups capable of reaction with the m nucleophilic groups to form covalent bonds, wherein $n \geq 2$ and $m + n \geq 5$;

(c) applying the first and second crosslinkable components to a first surface; and

(d) contacting the first surface with the second surface to effect adhesion therebetween,

wherein each crosslinkable component is biocompatible, synthetic, and nonimmunogenic.

94. The method of claim 93, wherein step (c) comprises simultaneously applying the first and second crosslinkable components to the first surface.

95. The method of claim 94, wherein prior to step (c), the first and second crosslinkable components are admixed to provide a reaction mixture and initiate crosslinking, and step (c) comprises applying the reaction mixture to the first surface and allowing crosslinking to proceed *in situ*.

96. The method of claim 93, wherein the first crosslinkable component is in an aqueous solution.

97. The method of claim 93, wherein at least one of the first and second surfaces is a native tissue surface.

98. A method for introducing a biocompatible, nonimmunogenic composition into a tissue within a body of a mammalian subject, comprising:

(a) providing a first crosslinkable component having m nucleophilic groups, wherein $m \geq 2$;

(b) providing a second crosslinkable component having n electrophilic groups capable of reaction with the m nucleophilic groups to form covalent bonds, wherein $n \geq 2$ and $m + n \geq 5$;

(c) applying the first and second crosslinkable components to the tissue; and

(d) allowing the first and second crosslinkable components to crosslink *in situ*,

wherein each crosslinkable component is biocompatible, synthetic, and nonimmunogenic.

99. The method of claim 98, wherein step (c) comprises simultaneously applying the first and second crosslinkable components to the tissue.

100. The method of claim 99, wherein prior to step (c), the first and second crosslinkable components are admixed to provide a reaction mixture and initiate crosslinking, and step (c) comprises applying the reaction mixture to the tissue.

101. A method for preventing the formation of adhesions following surgery or injury, comprising:

(a) providing a first crosslinkable component having m nucleophilic groups, wherein $m \geq 2$;

(b) providing a second crosslinkable component having n electrophilic groups capable of reaction with the m nucleophilic groups to form covalent bonds, wherein $n \geq 2$ and $m + n \geq 5$;

(c) applying the first and second crosslinkable components to the tissues comprising, surrounding, and/or adjacent to a wound resulting from surgery or injury; and

(d) allowing the components to crosslink *in situ*,

wherein each crosslinkable component is biocompatible, synthetic, and nonimmunogenic.

102. The method of claim 101, wherein step (c) comprises simultaneously applying the first and second crosslinkable components to the tissues.

103. The method of claim 102, wherein prior to step (c), the first and second crosslinkable components are admixed to provide a reaction mixture and initiate crosslinking,

and step (c) comprises applying the reaction mixture to the tissues.

104. A method for effecting the augmentation of tissue within the body of a mammalian subject, comprising:

(a) providing a first crosslinkable component having m nucleophilic groups, wherein $m \geq 2$;

(b) providing a second crosslinkable component having n electrophilic groups capable of reaction with the m nucleophilic groups to form covalent bonds, wherein $n \geq 2$ and $m + n \geq 5$;

(c) applying the first and second crosslinkable components to a tissue site in need of augmentation; and

(d) allowing the components to crosslink *in situ* to provide tissue augmentation,

wherein each crosslinkable component is biocompatible, synthetic, and nonimmunogenic.

105. The method of claim 104, wherein step (c) comprises simultaneously applying the first and second crosslinkable components to the tissue site in need of augmentation.

106. The method of claim 105, wherein prior to step (c), the first and second crosslinkable components are admixed to provide a reaction mixture and initiate crosslinking, and step (c) comprises applying the reaction mixture to the tissue site in need of augmentation.

107. The method of claim 104, wherein the tissue site is comprised of soft tissue.

108. The method of claim 104, wherein the tissue site is comprised of hard tissue.

109. A method for providing a biocompatible, nonimmunogenic coating on the surface

of a synthetic implant, comprising:

(a) providing a first crosslinkable component having m nucleophilic groups, wherein m $\geq 2$;

(b) providing a second crosslinkable component having n electrophilic groups capable of reaction with the m nucleophilic groups to form covalent bonds, wherein $n \geq 2$ and $m + n \geq 5$;

(c) applying the first and second crosslinkable components to a surface of a synthetic implant to provide a coating thereon; and

(d) allowing the components to crosslink *in situ* to provide a synthetic implant coated with a biocompatible, nonimmunogenic composition,

wherein each crosslinkable component is biocompatible, synthetic, and nonimmunogenic.

110. The method of claim 109, wherein step (c) comprises simultaneously applying the first and second crosslinkable components to the surface of the synthetic implant to provide a coating thereon.

111. The method of claim 110, wherein prior to step (c), the first and second crosslinkable components are admixed to provide a reaction mixture and initiate crosslinking, and step (c) comprises applying the reaction mixture to the surface of the synthetic implant to provide a coating thereon.

112. The method of claim 111, wherein the reaction mixture has a net neutral charge.

113. The method of claim 109, wherein the synthetic implant is an artificial blood vessel, a heart valve, a vascular graft, a vascular stent, or a vascular graft/stent combination.

114. The method of claim 109, wherein the synthetic implant is an implantable surgical

membrane.

115. The method of claim 114, wherein the implantable surgical membrane is monofilament polypropylene.

116. The method of claim 114, wherein the implantable surgical membrane is a mesh for use in hernia repair.

117. The method of claim 109, wherein the synthetic implant is a breast implant.

118. The method of claim 109, wherein the synthetic implant is a lenticule.

119. A synthetic implant coated according to the method of claim 109.

120. The crosslinkable system of claim 87, wherein the first crosslinkable component is present in a molar excess relative to the second crosslinkable component.

121. A method for preparing a negatively charged compound-containing matrix useful for delivery of a negatively charged compound to a mammalian subject, comprising:

(a) providing the crosslinkable system of claim 102;

(b) admixing the crosslinkable components in an acidic, aqueous medium to initiate crosslinking and form a crosslinked matrix with an excess of positively charged nucleophilic groups; and

(c) contacting the positively charged crosslinked matrix with the negatively charged compound to allow ionic binding therebetween.

122. The crosslinkable system of claim 87, wherein the second crosslinkable component is present in a molar excess relative to the first crosslinkable component.

123. A method for preparing a positively charged compound-containing matrix useful for delivery of a positively charged compound to a mammalian subject, comprising:

(a) providing the crosslinkable system of claim 122;

(b) admixing the crosslinkable components in a basic, aqueous medium to initiate crosslinking and form a crosslinked matrix with an excess of negatively charged electrophilic groups; and

(c) contacting the negatively charged crosslinked matrix with the positively charged compound to allow ionic binding therebetween.

124. The negatively charged compound-containing matrix prepared by the method of claim 121.

125. The positively charged compound-containing matrix prepared by the method of claim 123.

126. The composition of claim 66, further including an imaging agent.

127. A composition for administration of a biologically active agent to a mammalian subject, comprising:

(a) a first crosslinkable component having m nucleophilic groups, wherein $m \geq 2$;

(b) a second crosslinkable component having n electrophilic groups capable of reaction with the m nucleophilic groups to form covalent bonds, wherein $n \geq 2$ and $m + n \geq 5$; and

(c) a therapeutically effective amount of a biologically active agent selected from the group consisting of enzymes, receptor antagonists, receptor agonists, hormones, growth factors, autogenous bone marrow, antibiotics, antimicrobial agents, antibodies, cells and genes,

wherein the first and second crosslinkable components are biocompatible, synthetic, and nonimmunogenic.

128. The composition of claim 127, wherein the biologically active agent reacts with the first crosslinkable component, the second crosslinkable component, or both.

129. A method for treating a vascular malformation, comprising:

(a) providing a first crosslinkable component having m nucleophilic groups, wherein $m \geq 2$;

(b) providing a second crosslinkable component having n electrophilic groups capable of reaction with the m nucleophilic groups to form covalent bonds, wherein $n \geq 2$ and $m + n \geq 5$;

(c) admixing the crosslinkable components to provide a reaction mixture and initiate crosslinking;

(d) thereafter extruding or molding the admixture into a selected shape;

(e) dehydrating the shaped admixture to provide a dehydrated, shaped matrix; and

(f) delivering the dehydrated, shaped matrix to the site of the vascular malformation, thereby allowing repair thereof,

wherein the first and second crosslinkable components are biocompatible, synthetic, and nonimmunogenic.

130. A dehydrated, shaped matrix useful in the treatment of a vascular malformation, prepared by the method comprising:

(a) providing a first crosslinkable component having m nucleophilic groups, wherein $m \geq 2$;

(b) providing a second crosslinkable component having n electrophilic groups capable of reaction with the m nucleophilic groups to form covalent bonds, wherein $n \geq 2$ and $m + n \geq 5$;

(c) admixing the crosslinkable components to provide a reaction mixture and initiate crosslinking;

(d) thereafter extruding or molding the admixture into a selected shape; and

(e) dehydrating the shaped admixture to provide a dehydrated, shaped matrix adapted to be delivered to the site of the vascular malformation,

wherein the first and second crosslinkable components are biocompatible, synthetic, and nonimmunogenic.

131. A method for providing a biocompatible, nonimmunogenic coating on the interior surface of a physiological lumen, comprising:

(a) providing a first crosslinkable component having m nucleophilic groups, wherein m $\geq 2$,

(b) providing a second crosslinkable component having n electrophilic groups capable of reaction with the m nucleophilic groups to form covalent bonds, wherein $n \geq 2$ and $m + n \geq 5$,

(c) admixing the crosslinkable components to provide a reaction mixture and initiate crosslinking;

(d) immediately thereafter, applying a coating of the reaction mixture to the interior surface of a physiological lumen; and

(e) allowing the components to crosslink *in situ*,

wherein the first and second crosslinkable components are biocompatible, synthetic, and nonimmunogenic.--